All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

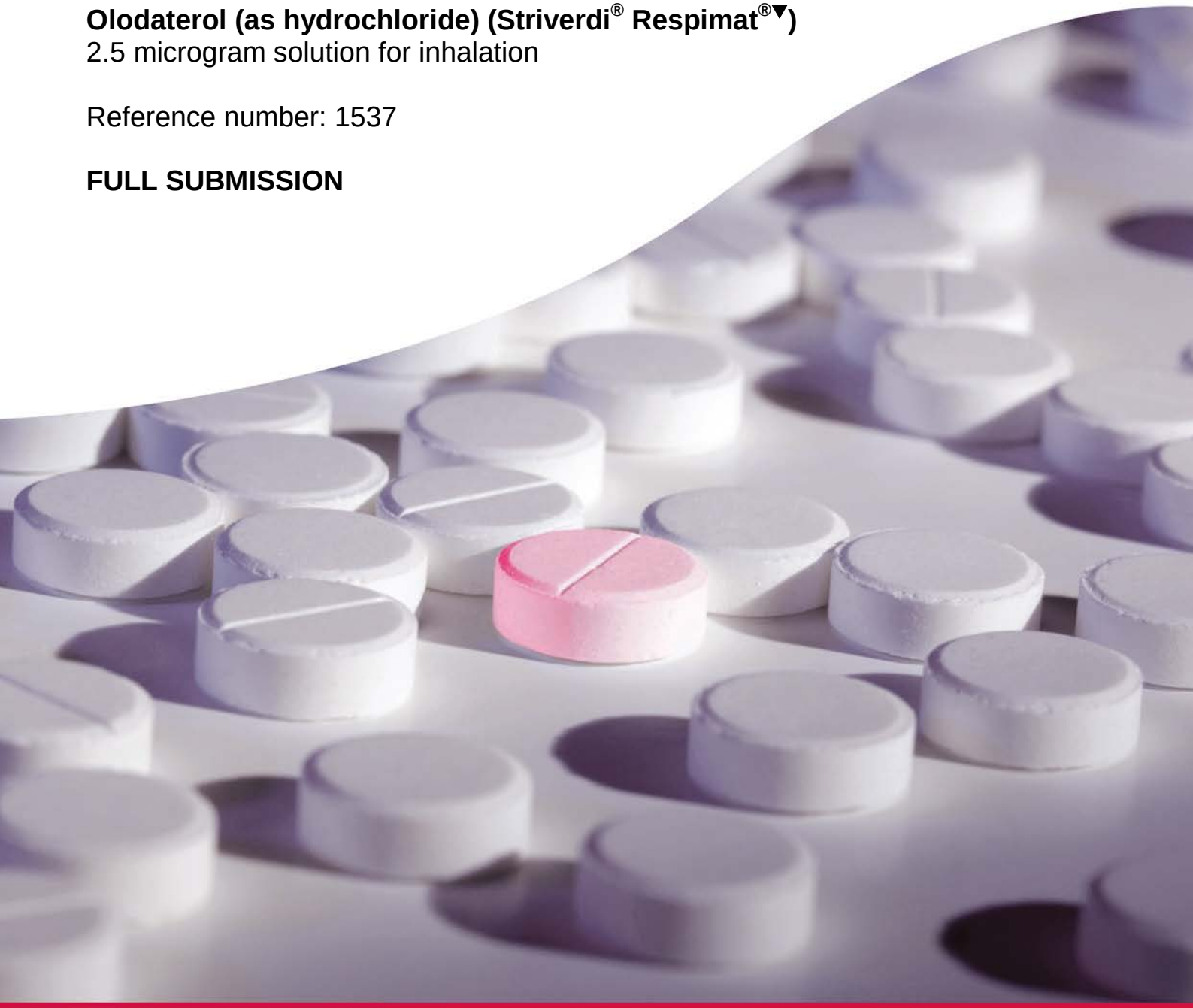
AWMSG SECRETARIAT ASSESSMENT REPORT

Olodaterol (as hydrochloride) (Striverdi® Respimat®▼)

2.5 microgram solution for inhalation

Reference number: 1537

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Olodaterol (as hydrochloride) (Striverdi® Respimat®▼) 2.5 microgram solution for inhalation

This assessment report is based on evidence submitted by Boehringer Ingelheim Ltd on 6 June 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Olodaterol (as hydrochloride) (Striverdi® Respimat®▼) is indicated as a maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)[2].
Dosing	The recommended dose is two puffs of 2.5 micrograms of olodaterol once daily, at the same time of day, using the Striverdi® Respimat®▼ inhaler[2].
Marketing authorisation date	10 October 2013[2].

2.0 DECISION CONTEXT

2.1 Background

Chronic obstructive pulmonary disease (COPD) is characterised by consistent airflow obstruction, which is usually progressive and not fully reversible[3]. This is associated with persistent and progressive breathlessness, a chronic productive cough and limited exercise capacity. COPD can be used to describe a number of conditions, such as chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation[3]. Smoking is the main cause of COPD, but other workplace exposures are likely to contribute such as dust, fumes and certain chemicals[4]. It is estimated that three million people have COPD in the UK, of which approximately 900,000 have been diagnosed[5]. The number of patients diagnosed with COPD in Wales in 2012–2013 was 67,773[6]. COPD prevalence increases with age and is rarely seen in people under the age of 35 years[3].

COPD treatment aims to reduce symptoms, lower the frequency and severity of exacerbations, improve health status and increase exercise tolerance[7]. Short-acting bronchodilators, including beta$_2$-agonist and muscarinic antagonist (anticholinergic) inhalation therapies, are central to the management of COPD symptoms[7]. For patients with stable COPD, who remain breathless or have exacerbations despite using short-acting bronchodilators, maintenance therapy in patients with a forced expiratory volume in 1 second (FEV_1) ≥ 50% is with a long-acting beta$_2$-agonist (LABA) or a long-acting muscarinic antagonist (LAMA). Maintenance therapy in patients with a FEV_1 < 50% is with a LABA and corticosteroid combination inhaler or a LAMA[5]. Olodaterol is a once-daily LABA, licensed to treat patients with COPD[2].

2.2 Comparators

The comparators included in the company submission were:

- Indacaterol (Onbrez® Breezhaler®).
- Formoterol (Foradil® Aerolizer®).
- Salmeterol (non proprietary).

2.3 Guidance and related advice

- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD (updated 2014)[7].
- National Institute for Health and Care Excellence (NICE) Pathways. Inhaled therapy in COPD (2013)[8].
- NICE. Chronic obstructive pulmonary disease. Clinical Guideline (CG) 101 (2010)[5] replaces CG 12 (2004)[9].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the fixed dose combination of indacaterol/glycopyrronium (Ultibro® Breezhaler®▼)[10]. AWMSG advice is pending for the fixed dose combination of umeclidinium/vilanterol (as trifenatate) (Anoro® Ellipta®▼)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of five pairs of phase III clinical studies[1]. Two pairs (1222.13 and 1222.14; 1222.24 and 1222.25) investigated the efficacy and safety of olodaterol compared with placebo and twice daily formoterol in patients with moderate to severe COPD and one pair (1222.39 and 1222.40) compared olodaterol with tiotropium bromide. The remaining two pairs (1222.11/12 and 1222.37/38) did not compare olodaterol with a LABA or a LAMA and therefore will not be discussed further in the clinical effectiveness section. The licensed dose of olodaterol hydrochloride is 5 micrograms and therefore the efficacy results of the 10 micrograms treatment arm are not reported in the clinical effectiveness section. In the absence of a direct comparison with indacaterol or salmeterol the company also provided network meta-analyses (NMAs) to make adjusted indirect treatment comparisons (ITCs)[1].

3.1 Study 1222.13 and 1222.14

These two studies were identical, randomised, double-blind, double-dummy, placebo-controlled, parallel group, multi-centre studies of 48 weeks duration comparing once daily orally inhaled olodaterol (5 micrograms) delivered by the Striverdi® Respimat®▼ inhaler with twice daily orally inhaled formoterol (Foradil®) 12 micrograms delivered by the Aerolizer® inhaler, in patients with COPD[12–14].

The study group consisted of patients aged ≥ 40 years with a diagnosis of COPD who met the following criteria: relatively stable airway obstruction with a post-bronchodilator FEV_1 < 80% of predicted normal and a post-bronchodilator FEV_1/Forced vital capacity (FVC) < 70% (see Glossary) at visit 1 (i.e. GOLD Stage II–IV patients). Patients were current or ex-smokers with a smoking history of > ten pack-years (see Glossary)[12–14].

The co-primary endpoints included trough FEV_1, FEV_1 area under the curve $(AUC)_{0\text{-}3h}$ response and Transition Dyspnoea Index (TDI) focal score (see Glossary) after 24 weeks of treatment[1,12–14]. For the combined study population (1222.13/14) there was no significant difference between olodaterol and formoterol for FEV_1 $AUC_{0\text{-}3h}$ response at week 24. There were significant increases in trough FEV_1 for both olodaterol and formoterol compared with placebo (commercial in confidence figures removed). The TDI focal scores could not be considered as a combined dataset as the results were not comparable. The differences in TDI focal scores were not significant for olodaterol versus placebo or formoterol versus placebo. Patients treated with olodaterol showed a statistically significant improvement (decrease) in the St George's Respiratory Questionnaire total score (SGRQ [see Glossary]) compared with placebo (-2.8 p = 0.0034), whereas there was no significant difference for formoterol compared with placebo (-1.248, p = 0.2009). A similar improvement in patient's global rating (PGR) was shown in the olodaterol group compared with formoterol (p = 0.9225). There was no statistically significant difference in the number of exacerbations or time to exacerbation between olodaterol or formoterol versus placebo. The results of the

secondary endpoints: SGRQ, PGR, number of exacerbations and time to exacerbation have to be considered as descriptive only due to the hierarchical testing model used.

3.2 Study 1222.24 and 1222.25

These two studies were identical, randomised, double-blind, double-dummy, placebo controlled, four-way cross-over multi-centre studies of six weeks duration comparing once daily orally inhaled olodaterol (5 micrograms) delivered by the Striverdi® Respimat®▼ inhaler with six weeks of twice daily formoterol 12 micrograms (Foradil®) delivered by the Aerolizer® inhaler, in patients with COPD[1,15–17]. The inclusion criteria were identical to studies 1222.13 and 1222.14 (see section 3.1).

The co-primary endpoints were FEV_1 $AUC_{0\text{-}12h}$ and FEV_1 $AUC_{12\text{-}24h}$ responses after six weeks. For the combined study population (1222.24/25) there was no significant difference in the adjusted mean difference between olodaterol and formoterol treatment groups for FEV_1 $AUC_{0\text{-}12h}$ response but there was a statistically significant difference between olodaterol and formoterol treatment groups for FEV_1 $AUC_{12\text{-}24h}$ response (commercial in confidence figures removed). There were no statistically significant differences between olodaterol and formoterol for the secondary endpoints (trough FEV_1 response, FEV_1 $AUC_{0\text{-}3h}$, and FEV_1 $AUC_{0\text{-}24h}$) [1,15–17].

Table 1. Overview of endpoints from combined study pairs 1222.13/14 and 1222.24/25.

		Adjusted mean difference versus placebo (95% CI)		Adjusted mean difference (95% CI)
	N	Olodaterol	Formoterol	Olodaterol vs. formoterol
Study 1222.13/14*				
Trough FEV_1 response (l)†	Placebo = 437 Olodaterol = 449 Formoterol = 444	§§ §§ §§	§§ §§ §§	§§ §§ §§
FEV_1 $AUC_{0\text{-}3h}$ (l)†	Placebo = 450 Olodaterol = 452 Formoterol = 455	§§ §§ §§	§§ §§ §§	§§ §§ §§
TDI focal score†§	Placebo = 192 Olodaterol = 212 Formoterol = 202	§§ §§ §§	§§ §§ §§	§§ §§ §§
TDI focal score†¶	Placebo = 221 Olodaterol = 221 Formoterol = 215	§§ §§ §§	§§ §§ §§	§§ §§ §§
Study 1222.24/25**				
Trough FEV_1 response (l) ††	Placebo = 184 Olodaterol = 184 Formoterol = 180	0.102 §§ §§	0.108 §§ §§	§§ §§ §§
FEV_1 $AUC_{0\text{-}12h}$ response (l)†		§§ §§ §§	§§ §§ §§	§§ §§ §§
FEV_1 $AUC_{12\text{-}24h}$ response (l)†		§§ §§ §§	§§ §§ §§	§§ §§ §§

*At week 24.
†Primary endpoint.
§Results for study 1222.13.
¶Results for study 1222.14.
**At week 6.
††Secondary endpoint.
§§Commercial in confidence.
CI: confidence interval; FEV/AUC: see Glossary; l: litre; NR: not reported; TDI: see Glossary.

3.3 Studies 1222.39 and 1222.40

These two studies were identical, randomised, double-blind, double-dummy, placebo-controlled, four-way cross-over multi-centre studies of six weeks duration comparing once daily orally inhaled olodaterol (5 micrograms) delivered by the Striverdi® Respimat®▼ inhaler with once daily orally inhaled tiotropium bromide 18 micrograms (Spiriva®) delivered by the Handihaler®. The co-primary endpoints were FEV_1 $AUC_{0\text{-}12h}$ and FEV_1 $AUC_{12\text{-}24h}$ responses after six weeks[1,15–17]. The inclusion criteria were identical to studies 1222.13/14 (see section 3.1). There were no statistically significant differences in the adjusted mean difference versus placebo of $FEV_1AUC_{0\text{-}12h}$ between olodaterol and tiotropium in the combined analysis (commercial in confidence figures removed) or in the adjusted mean difference versus placebo of FEV_1 $AUC_{12\text{-}24h}$/l in the combined analysis between olodaterol and tiotropium (−0.002 p = 0.9093 [−0.028 to 0.025]) [1,15–17].

3.4 Network meta-analyses

3.4.1 Olodaterol versus indacaterol

The applicant company conducted a systematic literature review of randomised, controlled clinical trials (RCTs) in patients with COPD to evaluate the efficacy and safety of olodaterol 5 micrograms and indacaterol 150 micrograms. A mixed treatment comparison (MTC) and adjusted indirect comparison were employed to evaluate treatment efficacy using outcome measures based on trough $FEV_{1,}$ TDI, SGRQ total score and response, rescue medication use (e.g. as needed salbutamol) and proportion of patients with exacerbations. No differences were reported for olodaterol and indacaterol in the change from baseline in trough FEV_1 in both the trials which excluded concomitant use of a LAMA and in those trials in which a LAMA was co-administered. The indirect comparison results showed no difference between olodaterol 5 micrograms and indacaterol 150 micrograms in TDI, change from baseline in SGRQ total score, change from baseline in rescue medication (puffs per day), and in the proportion of patients with exacerbations[1].

3.4.2 Olodaterol versus salmeterol

Two published network meta-analyses were used to identify relevant trials for the indirect treatment comparison and, screening was performed to select only those trials that would contribute relevant data. An adjusted indirect comparison (Bucher analysis) of RCTs in patients with COPD was undertaken to evaluate the relative efficacy and safety of olodaterol 5 micrograms compared with salmeterol 50 micrograms, linked with placebo as the common treatment comparator. Analyses were performed for the change from trough FEV_1 and SGRQ from placebo at six months for the overall patient population and for two patient subgroups: with and without LAMA treatment (see Table 2)[1].

No statistically significant differences were reported between olodaterol 5 micrograms and salmeterol 50 micrograms in the change from placebo in trough FEV_1 after six months for both subgroups (see table 2). There was a significantly greater treatment benefit (a negative change in SGRQ indicates benefit) amongst patients treated with olodaterol compared to patients treated with salmeterol (−1.647) in the subgroup without LAMA treatment. This numerical benefit was also displayed in the subgroup with LAMA treatment (−0.0463) and for the overall population (−1.98079) but was not statistically significant (95% confidence intervals [CIs] overlap zero)[1].

Table 2. Mean difference between olodaterol versus salmeterol in change in trough FEV_1/l versus placebo at six months.

Population	Adjusted mean difference versus placebo in trough FEV_1/l (95% CI)
Without LAMA treatment (fixed effects)	−0.018 (−0.046 to 0.011)
With LAMA treatment (random effects)	0.009 (−0.055 to 0.073)
Overall population (random effects)	−0.005 (−0.035 to 0.024)
CI: confidence interval; FEV: see Glossary; LAMA: long-acting muscarinic antagonist; l: litre.	

3.5 Comparative safety

The safety data in the submission were presented as a combined analysis of the 48-week parallel studies 1222.11/12/13/14 (n = 2,221) and a combined analysis of the six-week cross-over studies 1222.24/25/37/38/39/40 (n=1,589). In the combined parallel-group studies 1222.11/12/13/14 (which included treatment with the unlicensed olodaterol ten micrograms dose), the frequency of AEs experienced with olodaterol was comparable to both placebo and formoterol. Treatment related AEs were higher in both the placebo and formoterol arms than the olodaterol arm.(commercial in confidence figures removed). The number of patients who had fatal events in the olodaterol, formoterol and placebo groups were 13 (1.5%), 10 (2.2%) and 13 (1.5%). The general pattern of AEs reported in the combined 6-week cross-over studies 1222.24/25/37/38/39/40 was consistent with that seen for the 48-week, parallel-group studies[1]. For studies 1222.39/40 the number of treatment related AEs were the same for tiotropium and olodaterol (3 [1.4%]). There were no fatal events in these studies.

In the systematic review comparing olodaterol with indacaterol there was a non-significant difference in the relative risk of discontinuation due to an adverse event[1]. The adjusted indirect comparison comparing olodaterol and salmeterol did not indicate any significant difference between olodaterol and salmeterol in the AE risk ratios[1].

3.6 AWTTC critique

- The company were unable to provide direct clinical evidence comparing the efficacy of olodaterol versus indacaterol (a once-daily LABA), salmeterol, glycopyrronium or aclidinium.
- There were no statistically significant differences in FEV_1 $AUC_{0\text{-}3h}$ between olodaterol and formoterol at week 24 in studies 1222.13/14 and 1222.24/25.
- The olodaterol studies permitted the use of concomitant pulmonary medications (LAMAs, short-acting muscarinic antagonist, xanthines and inhaled corticosteroids). The studies may not reflect clinical practice where LABAs are used alone in line with NICE guidance. The use of a LABA and a LAMA is recommended in NICE guidance in situations where an inhaled corticosteroid is declined or not tolerated and the olodaterol studies did not reflect this place in therapy[5].
- In the absence of any direct comparative data for olodaterol versus indacaterol and salmeterol, the applicant company conducted NMA/adjusted ITCs. In the NMA/adjusted ITCs there were differences in study design with respect to allowed concomitant COPD medication and in the severity of patients enrolled. The company acknowledges the heterogeneity of the studies included in the analysis, and the inherent limitations of this approach[1]. Conclusions drawn from the NMA/adjusted ITCs should be considered in light of these limitations.

- Olodaterol provides an alternative choice of a once daily LABA and an alternative choice of inhaler device for the patient.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost minimisation analysis (CMA) of once daily olodaterol 5 micrograms compared against once daily indacaterol 150 micrograms and twice daily salmeterol 50 micrograms as maintenance bronchodilator treatment in patients with COPD.

In the absence of direct comparative efficacy data for olodaterol and indacaterol, NMA/adjusted ITCs have been conducted using data from clinical study reports of RCTs of olodaterol and published studies of indacaterol identified via a systematic literature review with a search date up to 2011 (see section 3.4)[1]. Where data permitted, these sought to compare the change from baseline in trough FEV_1 at weeks 6 or 12, change from baseline in SGRQ total score and the proportion of SGRQ responders (4 point decrease) at 12 weeks, TDI score at 12 weeks, use of short-acting rescue medication, and the proportion of patients experiencing exacerbations and the proportion of patients who discontinued treatment due to AEs over 24 weeks. Separate analyses for trough FEV_1 were conducted among studies that permitted or excluded concomitant use of LAMA, and all other outcomes were assessed using data from the included studies irrespective of LAMA use[1]. Adjusted ITCs of olodaterol and salmeterol for change from baseline in trough FEV_1 and SGRQ scores, and the proportion of patients who discontinued treatment due to AEs over 24 weeks, have also been conducted using olodaterol study data[1] and salmeterol data included in published meta-analyses[18,19].

The NMA/adjusted ITCs observed no statistically significant differences between olodaterol 5 micrograms and indacaterol 150 micrograms once daily for any of the above outcomes, no statistically significant difference between olodaterol 5 micrograms once daily and salmeterol 50 micrograms twice daily for FEV_1 outcomes and discontinuations due to AEs, and a statistically significant benefit for olodaterol over salmeterol in some of the SGRQ score analyses. Based on these results, the company considers olodaterol to be therapeutically equivalent to the comparators, and the CMA therefore considers only drug acquisition costs over one year. Current list prices for olodaterol, indacaterol and the Serevent® brand of salmeterol are used.

4.1.2 Results

The company's estimates of annual costs of olodaterol and the comparators are presented in Table 3. Olodaterol is estimated to be cost saving by around £35 per patient treated per year compared with both indacaterol 150 micrograms once daily and salmeterol 50 micrograms twice daily.

Table 3. Results of base case CMA.

Treatment	Cost per patient per day	Incremental cost per patient per day	Cost per patient per year	Incremental cost per patient per year
Olodaterol 5 mcg once daily	£0.88	−£0.10	£320.59	−£35.41
Indacaterol 150 mcg once daily	£0.98		£356.00	
Salmeterol 50 mcg twice daily	£0.98		£356.00	
mcg: micrograms.				

The company has presented sensitivity analyses to explore the uncertainty in the estimates of relative risks for SGRQ response, exacerbations, and discontinuations due to AEs for olodaterol compared with indacaterol, by applying the 95% CI of the relative risks of these events to the price of olodaterol. Within the range of the 95% CI for the relative risk of SGRQ response, olodaterol remained cost saving. The cost differential within the range of the 95% CI for exacerbations ranged from −£114.91 to +£83.21, and within the range of the 95% CI for discontinuations due to AEs ranged from −£190.74 to +£152.88[1]. A more intuitive threshold analysis by the company indicates that the cost of olodaterol would need to increase by 11% for it to no longer be cost saving compared with indacaterol at current list prices.

4.1.3 AWTTC critique

As there are no direct comparative studies of olodaterol and the comparators, adjusted ITCs have been conducted. Based on these, olodaterol is estimated to have comparable efficacy and safety to indacaterol 150 microrgams once daily and salmeterol 50 micrograms twice daily. However, there are limitations to these analyses. The literature searches used to identify relevant studies are dated, different approaches have been used to compare olodaterol against indacaterol and against salmeterol, and there are several sources of heterogeneity among the included studies related to disease severity and use of concomitant medication. No analyses have been presented specific to the licensed 300 microgram daily dose of indacaterol. Collectively, there are several areas of uncertainty, which may not be explored in the context of a CMA that assumes therapeutic equivalence. However, under an assumption of therapeutic equivalence, olodaterol 5 micrograms once daily is less costly than indacaterol 150 micrograms or 300 micrograms once daily, and salmeterol 50 micrograms twice daily, based on current NHS list prices.

Key strengths of the economic evidence include:

- In the absence of direct comparative study data for olodaterol and the comparators, the company has conducted NMA/adjusted ITC of study data identified via systematic literature reviews.
- Heterogeneity among the included studies has been identified and explored, and analyses conducted to try to limit the impact of that heterogeneity.

Key limitations and uncertainties of the economic evidence include:

- There are no direct comparative data for olodaterol and indacaterol or salmeterol. ITC have been necessary, which are associated with several limitations:
  - The literature searches to identify comparator study data for the ITCs were conducted up to a cut-off date of 2011 and have not been updated to determine if more recent study evidence for the comparators is available. For example, the largest indacaterol study to date (INVIGORATE)[20], published in 2013, is not included in the NMA.

  - The inclusion criteria for the NMA for comparison of olodaterol against indacaterol differ from the inclusion criteria for the comparison against salmeterol, as the latter were based on those employed in previously published literature reviews. The comparisons against salmeterol rely on adjusted ITCs across only placebo-controlled study arms of olodaterol and salmeterol, which discards the data available from comparisons with other agents that would be relevant had salmeterol been included in the company's de novo NMA.
  - Heterogeneity among the studies included in the NMA exists due to differences in enrolled patient disease severity and permitted concomitant treatments. The presence of heterogeneity may lead to biased estimates of treatment effect. CIs around outcome estimates are overlapping for olodaterol and the comparators in nearly all the indirect analyses, which the company suggests is evidence of comparable efficacy[1]; however, these CIs are wide (e.g. the 95% CI for SGRQ total score is compatible with indacaterol having a clinically meaningful improvement of 4.4 points compared with olodaterol, and a clinically non-meaningful worsening of 2.0 points). The relative effects of olodaterol on trough FEV_1 in patients who did not use concomitant LAMA are based on data from two six-week cross over studies, and analyses of all other outcomes are based on all included studies. Due to heterogeneity, the company notes these other analyses should be interpreted with caution.
- The sensitivity analyses regarding the uncertainty in the estimates of relative treatment effects are of limited informative value in the context of a CMA framework; the threshold analysis, which demonstrates that an 11% increase in the price of olodaterol would be required for cost neutrality, is more intuitive. Alternatively, a 10% decrease in the cost of indacaterol or salmeterol would be required for olodaterol to no longer be cost saving under an assumption of therapeutic equivalence.
- The company has compared olodaterol 5 micrograms against indacaterol 150 micrograms once daily. The indacaterol Summary of Product Characteristics notes that indacaterol 300 micrograms once daily has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD[21]. Although some of the studies included in the company's NMA included indacaterol 300 microgram arms, no specific analyses of olodaterol against indacaterol at a licensed dose of 300 micrograms once daily have been considered.
- No cost comparisons against formoterol, which is also licensed for use in COPD and was a study comparator for olodaterol, have been provided. Formoterol is administered twice daily and has a lower NHS list price than olodaterol and the other LABAs considered in the company's analyses.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost effectiveness of olodaterol.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Quality Outcomes Framework data, the company estimates that COPD patient population increased by an average of 2.61% per year between 2009–10 and 2012–13[6]. Applied to the 2012–13 figures, it is estimated there would be 71,354 COPD patients in Wales by the end of 2014, rising to 79,094 by the end of 2018. It is assumed

that these are net figures that account for patient mortality. Based on internal sales forecasts, the company anticipates that uptake in the first year post launch will mirror that observed with indacaterol, and will then remain constant over the next four years. Based on current NHS list prices, the company estimates cost savings of £35.41 per patient treated per year with olodaterol compared with either indacaterol or salmeterol. Assuming therapeutic equivalence and 100% adherence, the total cost savings in each of the next five years following the introduction of olodaterol are presented in Table 4.

5.1.2 Results

Table 4. Company budget impact estimates.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible COPD patients	71,354	73,215	75,125	77,084	79,094
Uptake (%)	*	*	*	*	*
Treated patients	*	*	*	*	*
Net costs (drug acquisition) per patient per year	**-£35.41**	**-£35.41**	**-£35.41**	**-£35.41**	**-£35.41**
Overall net costs	*	*	*	*	*
*Commercial in confidence.					

5.1.3 AWTTC critique

- The company has used Welsh-specific data to estimate the number of patients with COPD.
- Estimated uptake of olodaterol in the first year is reported to be based on that observed with indacaterol. Uptake estimates are a source of uncertainty in all budget impact estimates.
- The likely budget impact of use of olodaterol is subject to uncertainty; however, under the assumption of therapeutic equivalence, irrespective of the number of patients treated, use of olodaterol would be less costly than use of indacaterol and salmeterol at current list prices.

5.2 Comparative unit costs

Example comparative annual costs of olodaterol and alternative LABAs licensed for use in COPD, based on Drug Tariff list prices as of August 2014[22], are presented in Table 5. Where several formulations are available, the least costly product from the range, based on Drug Tariff prices, is provided. Combination products or concomitant agents that may be used routinely in the management of COPD (e.g. inhaled corticosteroids, LAMAs) are not included.

Table 5. Example annual costs of olodaterol and alternative LABAs for COPD.

Medicine	Example regimen	Annual cost*
Olodaterol 2.5 mcg solution for inhalation with device (Striverdi® Respimat®▼)	2 puffs once daily	£321†
Formoterol 12 mcg inhalation powder capsules with device (Foradil®)	1 puff twice daily	£291
Formoterol 12 mcg CFC-free inhaler (Atimos Modulite®)	1 puff twice daily	£219
Indacaterol 150 mcg or 300 mcg inhalation powder capsules with device (Onbrez® Breezhaler®)	1 puff once daily	£356
Salmeterol 25 mcg CFC-free inhaler (Serevent® Evohaler®)	2 puffs twice daily	£356
Salmeterol 50 mcg dry powder inhaler (Serevent Accuhaler®)	1 puff twice daily	£356

*Drug Tariff prices as of August 2014[22].
†Cost of olodaterol provided by the company[1].
This table does not imply therapeutic equivalence of medicines or doses.
See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,21,23–26].

mcg: micrograms.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, olodaterol (Striverdi® Respimat®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that olodaterol (Striverdi® Respimat®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 25 July 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Patient's global rating (PGR)
Patients completed a global rating assessment of their condition prior to pulmonary function testing. Patients were asked to rate their health (respiratory condition) at each visit, compared to the day before they commenced treatment with the study medicine. Their responses were recorded on a 7-point scale:
1: very much better
2: much better
3: a little better
4: no change
5: a little worse
6: much worse
7: very much worse

Pulmonary functional tests: Trough Forced Expiratory Volume (FEV_1), FEV_1 Area Under the Curve (AUC_{0-3h}), FEV_1 AUC_{0-12h} and FEV_1 AUC_{12-24h}
FEV_1 is the volume of air that can be forcefully and rapidly expired in 1 second, from a starting point of maximal inspiration, measured by a spirometer. FEV_1 is reduced in patients with COPD, and is well accepted by the scientific community and regulatory authorities as a marker of COPD severity. Trough FEV_1 is the measure taken in the morning prior to first dosing of any inhaled medications. FEV_1 AUC_{0-3h}, FEV_1 AUC_{0-12h} and FEV_1 AUC_{12-24h} refer to the difference in FEV_1 measurements taken between the stated hours post-dose in clinical studies of bronchodilators.

Forced Vital Capacity (FVC)
FVC is the volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume.

Smoking history
Current or ex-smokers with a smoking history of > ten pack-years (Pack-years = (Number of cigarettes per day/ 20 cigarettes per pack) x years of smoking.

St George's Respiratory Questionnaire (SGRQ)
The SGRQ is a 50-item questionnaire developed to measure health status (i.e. quality of life) in patients with diseases of airway obstruction, such as COPD. The total score is calculated from the scores in the three domains: Symptoms, Activity and Impacts (psycho-social). Psychometric testing has demonstrated its repeatability, reliability and validity; sensitivity has been demonstrated in clinical studies.

Transition Dyspnoea Index (TDI)
The Mahler Dyspnoea questionnaires allow investigators to document which daily activities cause the patient to feel breathless, and the level and extent at which activities could be performed.

To rate their change from baseline or the previous visit, patients report their impression of change which is recorded as a score from -3 to +3 for each of the three components of the TDI (intensity of breathlessness, magnitude of task, magnitude of effort), as described in Table 6; the scores for each component are then added to give an overall focal score from -9 to +9.

Table 6. TDI scoring: change from previous visit.

-3	-2	-1	0	+1	+2	+3
major deterioration	moderate deterioration	minor deterioration	no change	minor improvement	moderate improvement	major improvement

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